

January 28, 2002

Kathleen E. Lanshe
E.I. du Pont de Nemours & Co., Inc.
1007 Market Street
Wilmington, DE 19898

Dear Ms. Lanshe:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Dicarboxylic Acid Category, posted on the ChemRTK Web Site on September 13, 2001. I commend E.I. du Pont de Nemours & Co., Inc. and Solutia Inc. for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Chemical RTK HPV Challenge Program website EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the attached Comments on the Chemical RTK web site within the next few days. As noted in the comments, we ask that you advise the Agency, within 90 days of the posting on the Chemical RTK website, of any modifications to the submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit general questions about the HPV Challenge Program through the Chemical RTK web site comment button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
A. Abramson
C. Auer
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Dicarboxylic Acids

SUMMARY OF EPA COMMENTS

The sponsor, E.I. du Pont de Nemours & Co., Inc., submitted a test plan and robust summaries to EPA for the dicarboxylic acids category dated July 11, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on September 13, 2001. Dicarboxylic acids included in this group are succinic acid (CAS No. 110-15-6), glutaric acid (CAS No. 110-94-1), and adipic acid (CAS No. 124-04-9).

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The grouping of the three dicarboxylic acids into one category is supported by the information presented in the Test Plan.
2. Physicochemical and Environmental Fate Data. Data are adequate for the purposes of the HPV Challenge Program.
3. Health Endpoints. EPA agrees that the proposed reproductive toxicity screen would enhance the reproductive toxicity database. However, in accordance with HPV Challenge Program guidance, adequate evaluation of reproductive organs from available repeated-dose studies and the availability of the developmental toxicity studies may satisfy the reproductive/developmental toxicity endpoints. The submitter needs to provide detailed information on evaluation of reproductive organs from the repeated-dose toxicity studies.
4. Ecological Effects. EPA believes that the Submitter's use of a chemical mixture containing these chemicals to support the characterization of the chemicals needs to be strengthened. EPA disagrees that no additional fish toxicity information is needed to determine data adequacy and to satisfy the category approach for these chemicals. EPA considers the invertebrate and algal acute toxicity robust summaries adequate, but some data elements are missing (see specific comments on robust summaries). EPA suggests that the submitter consider using SAR to support the category approach or perform additional tests. EPA reserves judgement on the adequacy of the test plan pending revisions by the submitter.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON DICARBOXYLIC ACIDS CATEGORY CHALLENGE SUBMISSION

Category Definition

The Dicarboxylic Acid category consists of a homologous series of three substances: succinic, glutaric, and adipic acids.

Category Justification

The submitter bases this category on the structural similarities of the three substances, their physical and chemical properties, and aquatic and mammalian toxicities. The substances constitute a homologous series from C₄ to C₆ with identical functional groups. The measured physical and chemical properties for the three substances are generally similar or linear with molecular weight. From an environmental perspective, the solubilities of these chemicals are relatively high, estimated vapor pressures are low (< 3

X 10⁻⁶ mm Hg), and octanol/water partition coefficients are near or below one. The substances all biodegrade readily and have similar bioaccumulation and fugacity estimations.

The submitter did not provide any information about the composition of the dicarboxylic acid mixture used to support the category matrix pattern. In particular, for fish where there is insufficient data to read across, the use of the mixture data appears reasonable, however a countervailing factor is not mentioned, the much lower toxicity for the mixture in invertebrates (>1000 mg/L) compared to the 85.7 mg/L tested with adipic acid. Because a difference of this magnitude is not seen in the succinic acid toxicity to invertebrates, this may also be observed in a 96-hour fish test for succinic acid. Thus, it should not be implied that the toxicity of the mixture is similar to individual compounds or all aquatic species.

The health effects data provide support for inclusion of these chemicals in a category. Adequate developmental toxicity data were available for adipic and glutaric acid and indicated no differences. Results in genotoxicity assays were similar for all category members.

Supporting data were also provided for a mixture of these dicarboxylic acids, but the percent composition of this mixture was not provided and it is not clear if the same mixture was used in all of the tests.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

EPA agrees with the submitter's test plan for these endpoints.

Environmental Fate (photodegradation, stability in water, biodegradation, transport/distribution)

EPA agrees with the submitter's test plan for these endpoints.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive and developmental toxicity)

EPA agrees with the submitter's test plan that adequate data are available for acute toxicity, repeated-dose toxicity, genetic toxicity, and developmental toxicity.

Reproductive and Developmental Toxicity

The submitter concludes that developmental toxicity testing is not required based on test data that are adequate for glutaric acid and generally adequate for adipic acid; the two adipic acid studies did not include a high dose that caused maternal toxicity. For succinic acid, the submitter states that there are "no reliable data," and provides in Section 5.3 of the Robust Summaries several references for developmental studies, although none were summarized. The summarization of these studies, even though they were inadequate by themselves, would assist in the weight-of-evidence evaluation for this category.

The submitter reports that no effects on reproductive organs were observed in repeated-exposure studies of adipic and glutaric acid and proposes that a reproductive toxicity screen be performed on adipic acid. EPA agrees that the proposed reproductive toxicity screen would enhance the reproductive toxicity database. However, in accordance with HPV Challenge Program guidance, adequate evaluation of reproductive organs from available repeated-dose studies and the availability of the developmental toxicity studies may satisfy the reproductive/developmental toxicity endpoints. The submitter needs to provide detailed information on evaluation of reproductive organs from the repeated-dose toxicity studies.

Ecotoxicity (fish, daphnid, and algal toxicity)

EPA believes that the fish acute toxicity studies for glutaric and succinic acids are inadequate due to 24-hour instead of required 96-hour exposure durations to satisfy the read across category approach for fish. Also, EPA believes that the use of the data on the mixture to support the category approach needs to be strengthened. The submitter should consider using SAR to support the aquatic endpoints or perform additional tests. Guidance on the use of SAR can be found on the EPA Challenge Web site <http://www.epa.gov/chemrtk/sarfin1.htm>. Where appropriate data exist for fish, daphnia, and algae, the submitter needs to supply full robust summaries to include missing data elements to determine data adequacy (see specific comments on robust summaries).

Specific Comments on the Robust Summaries

The majority of the robust summaries gave incomplete reference citations for the evaluated studies and some are missing critical data elements. The submitter needs to provide full titles for all studies and additional identifying information (e.g. full date of report) for the unpublished industrial studies. EPA has provided specific comments on how to enhance the robust summaries to the standard established in EPA's HPV Challenge Program Guidance at <http://www.epa.gov/chemrtk/guidocs.htm>.

Health

Acute toxicity

The submitter needs to provide information on dose levels at which clinical symptoms were observed and severity or duration of symptoms.

Repeated-dose toxicity

In feeding studies, the submitter needs to provide doses in terms of mg/kg/body weight/day. In the summaries of two 2-year oral dosing studies (one for adipic acid, one for succinic acid) the submitter needs to provide information on clinical signs, clinical chemistry, and hematology, or indicate that these elements were not available.

Reproductive toxicity

Table 6 of the test plan indicates that this endpoint was fulfilled by the lack of adverse effects on reproductive organs in repeated exposure studies with adipic acid, glutaric acid, and dicarboxylic acid mixture. However, in the robust summaries, the submitter needs to provide information on the evaluation of the reproductive organs.

Developmental toxicity

In the robust summaries of the developmental toxicity studies the submitter needs to identify NOAELs and LOAELs for fetal and maternal toxicity in the Results section.

Ecotoxicity Studies

Adipic Acid

Fish. Missing data elements include, chemical purity, DO, and hardness.

Daphnia. Missing data elements include pH, hardness, DO, temperature, measured or nominal concentrations, number of replicates, number of tests, and chemical purity.

Algae. Missing data elements include, pH, temperature, hardness, measured or nominal concentrations, and chemical purity.

Glutaric Acid

Algae. Missing data elements include, pH, temperature, hardness, measured or nominal concentrations, and chemical purity.

Succinic Acid

Daphnia. Missing data elements include DO and chemical purity.

Algae. Missing data elements include, pH, temperature, hardness, measured or nominal concentrations, type of endpoint, duration of endpoint, and chemical purity.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.